CASWELL FILE

TXR # 0001425

PC 417300

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

FEB 18 1982

NOEL changed 3 → 31 mkd L Kanga

SPECIAL

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

DATE: February 9, 1982

SUBJECT: EPA Reg.#524-308; Lifetime Feeding Study in Rats with Glyphosate
CASWELL #661A Accession#246617-21

FROM: William Dykstra, Toxicologist WHD, 2/9/82
Toxicology Branch/HED (TS-769)

TO: Robert Taylor (25)
Registration Division (TS-767)

Recommendation:

1) The study is acceptable as Core-Minimum Data. The oncogenic potential is negative. The NOEL for chronic toxicity is the low-dose of 3.0 mg/kg/day.

Review:

1) A Lifetime Feeding Study of Glyphosate in Rats (Bio/dynamics Project No. 77-2062; 9/18/81)

Test Material: Glyphosate (technical); 98.7% a.i.; fine white powder; Lot#XHJ-64

Four groups of 50/sex/group, corresponding to controls, low-dose group, mid-dose group and high-dose group were employed in the study. The dosage level of test-material administered to each group was 0 (controls, Group 1) 30 ppm (low-dose, Group 2) 100 ppm (mid-dose Group 3) and 300 ppm (high-dose, Group 4) during the first week of the study. For the remainder of the study, dose levels of 3.05, 10.30 and 31.49 mg/kg/day for the males and 3.37, 11.22 and 34.02 mg/kg/day for the females were maintained. Termination occurred at 26 months (until survival had decreased to 30% in one group per sex).

All rats were observed twice daily for mortality and toxic signs and given a detailed physical examination each week throughout the study. Body weights and food consumption were determined at pretest, weekly through 14 weeks and biweekly thereafter. Water consumption was determined for 10 rats/sex/group for two separate three-day periods at 18 and 24 months.

The following clinical parameters were determined for 10 rats/sex/group at 4, 8, 12, 18 and 24 months: hematology included hemoglobin, hematocrit, erythrocytes, platelets, and total and differential leucocytes; blood biochemistry parameters included serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, alkaline phosphatase, lactic acid dehydrogenase, blood urea nitrogen, fasting glucose, cholesterol, total protein, albumin, globulin, total and direct bilirubin, potassium and calcium; urinalysis included gross appearance, specific gravity, pH, protein, glucose, ketones, bilirubin, occult blood and microscopic analysis.

Complete necropsies were performed on all rats that died or were sacrificed during or at the end of the study. Organ weights were recorded for adrenals, brain, heart, kidneys, liver, testes/ovaries, pituitary, spleen and thyroid. Microscopic examination of the following tissues was performed for all treated and control rats: abdominal aorta, adrenals, blood smear, bone, bone marrow, brain (3 sections), epididymides, esophagus, eyes with optic nerve and harderian glands, gonads, heart, cecum, colon, duodenum, ileum, jejunum, kidneys, liver, lungs (with bronchi), lymph nodes, mammary gland, nerve (sciatic), pancreas, parathyroid, pituitary, prostate, salivary gland, skeletal muscle, seminal vesicles, skin, spinal cord (cervical), spleen, stomach, thymus, thyroid, trachea, urinary bladder, uterus, gross lesions, tissue masses or suspect tumors. Three coronal sections through the head and a section of thoracic spinal cord from ten males and ten females of each group were also examined microscopically.

Results:

Survival was unaffected by treatment. Survival was greater than 50% for each sex of each group at 18 months.

Decreased body weight gains, although not statistically significant, were seen in treated males beginning at week 26 and continuing to week 102. The decreases reached 6% for high-dose males at week 74 and 2-3% for mid- and low-dose males during this growth period. Decreased body weight gains were statistically significantly (10-15%) reduced in the low- and mid-dose female rats from weeks 84 to 92.

No dose-response relationship was present in the decreased body weight gains in female rats. The changes in body weight did not affect survival.

Food consumption showed a few significant changes in males and females, but overall food consumption was unaffected by treatment.

Water consumption for males and females did not show a treatment-related effect.

Hematology, clinical chemistry, and urinalyses values of treated male and female rats were comparable to controls.

Absolute organ weights and relative organ weights of male and female treated rats were comparable to controls.

The results of gross necropsy did not reveal any treatment-related findings.

Microscopic examination revealed lymphocytic hyperplasia of the thymus occurring at statistically significant incidences in the mid- and high-dose female rats.

Another non-neoplastic lesion occurring at increased incidence was focal vacuolation of the liver in high-dose male rats.

Other microscopic findings in male and female treated rats were comparable to their respective controls.

Neoplastic lesions were comparable between the controls and treated groups.

However, the interestitial cell tumor in the testis of male rats was observed in the following groups as showed below:

Group I (control) 0/50
Group II (low-dose) 3/50
Group III (mid-dose) 1/50
Group IV (high-dose) 6/50

The occurrence of testicular interstitial tumors of 12% (6/50) in the high-dose group is statistically significant ($p = 0.013$).

To further examine these results, the historical control data for interstitial cell tumor of the testes were compiled. These control data include only those lifetime feeding studies with Charles River Sprague-Dawley rats conducted by Bio/dynamics Inc. which were tested concurrently with the present study, i.e., were completed within nine months of termination of the present study, and lasted at least 24 months. For all male animals on test (Table IV, page 10, Vol. 1), the high-dose group incidence in the present study of 12% (6/50) was slightly higher than the highest-concurrent control incidence of 7% (5/75) and higher than the overall incidence of 4.5% (24/535).

We agree with the interpretation of the testicular tumors given by Experimental Pathology Laboratories pathologist, Dr. Martin G. Strobl, (Vol. 2, page 4), who states:

"The significance, if any, of the 12% incidence of interstitial cell tumor in the testis in the high dose group of male rats in this study in comparison to the control group is not known. It may represent a biological variation in this strain of rats. The incidence of interstitial cell tumor in the testis in Group II and Group III of this study was similar to the incidence observed in the control groups of male rats in the other concurrent studies and did not appear to be related to the administration of the test compound in this study."

Conclusion:

Oncogenic potential is negative. The NOEL for chronic toxicity is 3.0 mg/kg/day (low-dose).

Classification: Core-Minimum Data

changed as per L. Kaza
EPL/BD → 31 mtcd

TS-769:th:TOX/HED:WDykstra:2-8-82:card #6

Test for Significance of Differences Between Proportions 2/5/82

Lymphocytic hyperplaasia

ppm	# RESP	Total	%	+/-2(S.D.)	One Tail P Statistic Fisher's
0.000	5	25	20.00	+/-(17.68)	
30.000	13	32	40.63	+/-(18.58)	0.084
100.000	18	37	48.65	+/-(17.46)	0.020
300.000	17	34	50.00	+/-(18.28)	0.017

Test for a linear trend is not significant

Test for Significance of Differences Between Proportions 2/4/82

Testicular tumors

ppm	# RESP	Total	% +/-2(S.D.)	One Tail P Statistic Fisher's
0.000	0	50	0.00+/-(1.00)	
30.000	3	50	6.00+/-(7.58)	0.121
100.000	1	50	2.00+/-(4.88)	0.500
300.000	6	50	12.00+/-(10.01)	0.013

Test for Linear Trend in Proportions P = 0.011

CASWELL FILE

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

TO: Robert Taylor, PM#25
Registration Division (TS-769)

SUBJECT: EPA Reg.#524-308; Lifetime Feeding Study in Rats with Glyphosate CASWELL#661A

Recommendation:

Further evaluation of the NOEL of the study in light of the submitted information indicates that the NOEL for chronic toxicity is 31 mg/kg/day (34 mg/kg/day, females) rather than 3.0 mg/kg/day as previously reported.

TDC 4/8/82

William Dykstra, Ph.D
Toxicology Branch
Hazard Evaluation Division (TS-769)

CASWELL

Monsanto

Monsanto Company
1101 17th Street, N.W.
Washington, D.C. 20036
Phone: (202) 452-8880

April 6, 1982

Director
Registration Division (TS767C)
Office of Pesticide Programs
Environmental Progection Agency
1921 Jefferson Davis Highway
Arlington, VA 22202

Attention: Mr. Robert J. Taylor
Product Manager (25)

Subject: ROUNDUP® Herbicide
EPA Reg. No. 524-308
Response to Agency review
of the Lifetime Chronic
Feeding Study in Rats
with Glyphosate; BDN 77-416,
B/d No. 77-2062

Dear Sir:

On January 14, 1982, Monsanto submitted to the Agency, a Lifetime Chronic Feeding Study of Glyphosate (ROUNDUP Technical) in Rats, BDN 77-416, accession numbers 246617 through 246621 inclusive. On March 1, 1982, you notified us that the scientific review and evaluation of this study had been completed and that the NOEL for chronic toxicity had been determined as 3.0 mg/kg/day, the lowest dietary level for the study. In response to our inquiry as to the basis for this NOEL, you provided an EPA memorandum report of February 9, 1982, from Dr. William Dykstra to Mr. Robert J. Taylor. Copies of this correspondence are attached.

We have thoroughly reviewed the issues involved and we maintain on the basis of the additional information provided herewith that the NOEL for chronic toxicity should be 31 mg/kg/day (34 mg/kg/day, females).

We have requested that the Board Certified pathologist who performed the histopathological evaluations for this study, Dr. M. Robl of Experimental Pathology Laboratories, Inc., outline in writing why he does not consider lymphocytic hyperplasia biologically significant. A copy of his response is enclosed.

In Monsanto's opinion this effect is not considered biologically significant because:

1. As stated by the pathologist, the thymus is not the organ of choice for definitive evaluation of lymphocytic hyperplasia. Therefore, it is most noteworthy that there was no increase in the incidence of this lesion in other lymphoreticular organs which would confirm that this effect in the thymus was related to treatment.

2. There was very little difference in the relative severity of this lesion in control and treated animals. The severity in almost all animals was graded as minimal to slight.

3. There was no evidence of any increase in lymphoreticular neoplasms among treated as compared to control animals.

4. A clear dose response was not evident and no changes in the hematology parameters due to compound administration were observed.

5. In a three-generation reproduction study with glyphosate in the same strain of rat conducted at the same laboratory (Bio/dynamics No. 77-2063; Assession #245409), there was no difference in the incidence of lymphocytic hyperplasia in the thymus or other lymphoreticular organs of treated and control F_0, F_1, or F_2 parental animals. The dosage levels used in the reproduction study were identical to those in the subject study.

In Monsanto's opinion, use of the proper statistical tools for evaluation of mathematical significance of lymphocytic hyperplasia in the subject study further supports the lack of biological significance of this effect. The incidences of this lesion in the three treated groups in the referenced study were compared to the control incidence by EPA reviewers using Fisher's Exact test. Apparently the Bonferroni Inequality correction factor (Miller, R.G., Simultaneous Statistical Inference, McGraw/Hill, 1966) was not used. This correction factor is generally applied when making multiple pair-wise comparisons to account for the random chance that any one comparison will be statistically significant in the absence of a true treatment effect. For any statistical comparison at the $p<0.05$ level, there is a 1 in 20 chance that a statistically significant difference will be found in the absence of a true effect. Subsequently, for

three comparisons at the $p<0.05$ level, there is a 3 in 20 chance that any one or more of these comparisons will be statistically significant in the absence of a true effect. In other words, the true probability level for each of the three comparisons is $p<3 \times 0.05$ or $p<0.15$. For this reason, this correction factor is routinely used for example in the analysis of NTP chronic bioassay data by NCI.

When the Bonferroni Inequality factor is applied for three comparisons, each comparison would be considered significantly different only if $p<0.05 \div 3$ or $p<0.017$. If this correction is applied to the comparison of the incidence of lymphocytic hyperplasia in the thymus in the subject study, the differences between the control and the mid- and low- (3 mg/kg/day) dose groups are not statistically significant, and the difference for the high- (30 mg/kg/day) dose group (i.e., $p = 0.0175$) is essentially at the level of significance ($p<0.017$).

We respectively request that you reconsider the NOEL for this study in view of the information submitted herein.

Since this letter, in the opinion of Monsanto Company, constitutes trade secret/and confidential or proprietary information, we request that your agency treat this information accordingly.

If you should have any questions concerning our position, we would be happy to discuss these issues personally at your convenience or by phone (314-694-8823). Also, we would encourage you to contact Dr. Robl (703-471-7060) if you should have any questions concerning his evaluation.

Sincerely,

Rick B. Oleson

Rick B. Oleson, D.Sc.
Senior Product Toxicology Specialist

RBO:sfe
Attachment
cc: D.N. Duncan
R.W. Street

13544

032727

Chemical:	**Glyphosate**
PC Code:	**417300**
HED File Code	**13000 Tox Reviews**
Memo Date:	**02/18/82**
File ID:	**00000000**
Accession Number:	**412-03-0107**

HED Records Reference Center
02/25/2003